AMENDMENTS TO THE SPECIFICATION

Please amend the following paragraphs in the specification as follows:

[0110] Particularly advantageous strategies for incorporating epitopes and/or epitope clusters, into a vaccine or pharmaceutical composition are disclosed in PCT Publication WO 01/82963 and U.S. Patent Application No. 09/560,465 (now abandoned) entitled "EPITOPE SYNCHRONIZATION IN ANTIGEN PRESENTING CELLS," filed on April 28, 2000, which are hereby incorporated by reference in their entireties. The teaching and embodiments disclosed in said PCT publication are contemplated as supporting principals and embodiments related to and useful in connection with the present invention. Epitope clusters for use in connection with this invention are disclosed in PCT Publication WO 01/82963 and U.S. Patent Application No. 09/561,571 entitled "EPITOPE CLUSTERS," filed on April 28, 2000, which are hereby incorporated by reference in their entireties. The teaching and embodiments disclosed in said PCT publication are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

[0117] The immunization with DNA requires that APCs take up the DNA and express the encoded proteins or peptides. It is possible to encode a discrete class I peptide on the DNA. By immunizing with this construct, APCs can be caused to express a housekeeping epitope, which is then displayed on class I MHC on the surface of the cell for stimulating an appropriate CTL response. Constructs generally relying on termination of translation or non-proteasomal proteases for generation of proper termini of housekeeping epitopes have been described in PCT Publication WO 01/82963 and U.S. Patent application No. 09/561,572 (now abandoned) entitled EXPRESSION VECTORS ENCODING EPITOPES OF TARGET-ASSOCIATED ANTIGENS, filed on April 28, 2000, which are hereby incorporated herein by reference in their entirety. The teaching and embodiments disclosed in said PCT publication are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

[0126] Additional guidance on nucleic acid constructs useful as vaccines in accordance with the present invention are disclosed in WO 01/82963 and U.S. Patent Application No. 09/561,572 (now abandoned) entitled "EXPRESSION VECTORS ENCODING EPITOPES OF TARGET-ASSOCIATED ANTIGENS," filed on April 28, 2000, both of which are hereby incorporated by reference in their entireties. Further, expression vectors and methods

for their design, which are useful in accordance with the present invention are disclosed in PCT Publication WO 03/063770; U.S. Patent Application No. 10/292,413 (now U.S. Patent Publication No. 2003-0228634), filed on November 7, 2002; and U.S. Provisional Application No. 60/336,968 ~~(attorney docket number CTLIMM.022PR)~~ entitled "EXPRESSION VECTORS ENCODING EPITOPES OF TARGET-ASSOCIATED ANTIGENS AND METHODS FOR THEIR DESIGN," filed on 11/7/2001; all of which are incorporated by reference in their entireties. The teaching and embodiments disclosed in said PCT publications are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

[0127] A preferred embodiment of the present invention includes a method of administering a vaccine including an epitope (or epitopes) to induce a therapeutic immune response. The vaccine is administered to a patient in a manner consistent with the standard vaccine delivery protocols that are known in the art. Methods of administering epitopes of TAAs including, without limitation, transdermal, intranodal, perinodal, oral, intravenous, intradermal, intramuscular, intraperitoneal, and mucosal administration, including delivery by injection, instillation or inhalation. A particularly useful method of vaccine delivery to elicit a CTL response is disclosed in Australian Patent No. 739189 issued January 17, 2002; PCT Publication No. WO 099/02183; U.S. Patent Application No. 09/380,534 (now U.S. Patent 6,994,851), filed on September 1, 1999; a Continuation-in-Part thereof U.S. Patent Application No. 09/776,232 (now U.S. Patent 6,977,074) both entitled "A METHOD OF INDUCING A CTL RESPONSE," filed on February 2, 2001, published as 20020007173; and PCT Publication No. WO 02/062368; all of which are incorporated herein by reference in their entireties. The teachings and embodiments disclosed in said publications and applications are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

[0146] PSMA (prostate-specific membranes antigen), a TuAA described in U.S. Patent 5,538,866 entitled "PROSTATE-SPECIFIC MEMBRANES ANTIGEN" which is hereby incorporated by reference in its entirety, is expressed by normal prostate epithelium and, at a higher level, in prostatic cancer. It has also been found in the neovasculature of non-prostatic tumors. PSMA can thus form the basis for vaccines directed to both prostate cancer and to the

neovasculature of other tumors. This later concept is more fully described in U.S. Patent Publication No. 20030046714; PCT Publication No. WO 02/069907; and a provisional U.S. Patent application No. 60/274,063 entitled ANTI-NEOVASCULAR VACCINES FOR CANCER, filed March 7, 2001, and U.S. Application No. 10/094,699 (now U.S. Patent 7,252,824), ~~attorney docket number CTLIMM.015A,~~ filed on March 7, 2002, entitled "ANTI-NEOVASCULAR PREPARATIONS FOR CANCER," all of which are hereby incorporated by reference in their entireties. The teachings and embodiments disclosed in said publications and applications are contemplated as supporting principals and embodiments related to and useful in connection with the present invention. Briefly, as tumors grow they recruit ingrowth of new blood vessels. This is understood to be necessary to sustain growth as the centers of unvascularized tumors are generally necrotic and angiogenesis inhibitors have been reported to cause tumor regression. Such new blood vessels, or neovasculature, express antigens not found in established vessels, and thus can be specifically targeted. By inducing CTL against neovascular antigens the vessels can be disrupted, interrupting the flow of nutrients to (and removal of wastes from) tumors, leading to regression.

[0153] The ED-B domain is also expressed in fibronectin of the neovasculature (Kaczmarek, J. et al. *Int. J. Cancer* 59:11-16, 1994; Castellani, P. et al. *Int. J. Cancer* 59:612-618, 1994; Neri, D. et al. *Nat. Biotech.* 15:1271-1275, 1997; Karelina, T.V. and A.Z. Eisen *Cancer Detect. Prev.* 22:438-444, 1998; Tarli, L. et al. *Blood* 94:192-198, 1999; Castellani, P. et al. *Acta Neurochir. (Wien)* 142:277-282, 2000). As an oncofetal domain, the ED-B domain is commonly found in the fibronectin expressed by neoplastic cells in addition to being expressed by the neovasculature. Thus, CTL-inducing vaccines targeting the ED-B domain can exhibit two mechanisms of action: direct lysis of tumor cells, and disruption of the tumor's blood supply through destruction of the tumor-associated neovasculature. As CTL activity can decay rapidly after withdrawal of vaccine, interference with normal angiogenesis can be minimal. The design and testing of vaccines targeted to neovasculature is described in Provisional U.S. Patent Application No. 60/274,063 entitled "ANTI-NEOVASCULATURE VACCINES FOR CANCER" and in U.S. Patent Application No. 10/094,699 (now U.S. Patent 7,252,824), ~~attorney docket number CTLIMM.015A,~~ entitled "ANTI-NEOVASCULATURE PREPARATIONS FOR CANCER, filed on date even with this application (March 7, 2002). A tumor cell line is

disclosed in Provisional U.S. Application No. 60/363,131, filed on March 7, 2002, ~~attorney docket number CTLIMM.028PR,~~ entitled "HLA-TRANSGENIC MURINE TUMOR CELL LINE," which is hereby incorporated by reference in its entirety.

[0157] All references mentioned herein are hereby incorporated by reference in their entirety. Further, incorporated by reference in its entirety is U.S. Patent Application No. 10/005,905 (now abandoned) ~~(attorney docket number CTLIMM.021CP1)~~ entitled "EPITOPE SYNCHRONIZATION IN ANTIGEN PRESENTING CELLS," filed on November 7, 2001 and a continuation thereof, U.S. Application No. 10/026,066 (now U.S. Patent Publication No. 2003-0215425), filed on December 7, 2000, ~~attorney docket number CTLIMM.21CP1C,~~ also entitled "EPITOPE SYNCHRONIZATION IN ANTIGEN PRESENTING CELLS."

[0161] The construction of three generic epitope expression vectors is presented below. The particular advantages of these designs are set forth in PCT Publication No. WO 01/82963 and U.S. Patent Application No. 09/561,572 (now abandoned) entitled "EXPRESSION VECTORS ENCODING EPITOPES OF TARGET-ASSOCIATED ANTIGENS," filed on April 28, 2000, which have been incorporated by reference in their entireties above. Additional vectors strategies for their design are disclosed in PCT Publication WO 03/063770; U.S. Patent Application No. 10/292,413 (now U.S. Patent Publication No. 2003-0228634), filed on November 7, 2002; and Provisional U.S. Patent application No. 60/336,968 entitled "EXPRESSION VECTORS ENCODING EPITOPES OF TARGET-ASSOCIATED ANTIGENS AND METHODS FOR THEIR DESIGN," filed on November 7, 2001, which were incorporated by reference in their entireties above. The teachings and embodiments disclosed in said PCT publications and applications are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.

[0211] Proteasome was isolated from human red blood cells using the proteasome isolation protocol described in PCT Publication No. WO 01/82963 and U.S. Patent Application No. 09/561,074 (now U.S. Patent No. 6,861,234) entitled "METHOD OF EPITOPE DISCOVERY," filed on April 28, 2000; both of which are incorporated herein by reference in their entireties. The teachings and embodiments disclosed in said PCT publication and application are contemplated as supporting principals and embodiments related to and useful in

connection with the present invention. SDS-PAGE, western-blotting, and ELISA were used as quality control assays. The final concentration of proteasome was 4 mg/ml, which was determined by non-interfering protein assay (Geno Technologies Inc.). Proteasomes were stored at -70°C in 25 µl aliquots.

[0406] Known and predicted epitopes are generally not evenly distributed across the sequences of protein antigens. As referred to above, we have defined segments of sequence containing a higher than average density of (known or predicted) epitopes as epitope clusters. Among the uses of epitope clusters is the incorporation of their sequence into substrate peptides used in proteasomal digestion analysis as described herein, or to otherwise inform the selection and design of such substrates. Epitope clusters can also be useful as vaccine components. Fuller discussions of the definition and uses of epitope clusters is found in PCT Publication No. WO 01/82963; PCT Publication No. WO 03/057823; and U.S. Patent Application No. 09/561,571 entitled EPITOPE CLUSTERS, which all are or were previously incorporated by reference in their entireties and in U.S. Patent Application No. 10/026,066 (now U.S. Patent Publication No. 2003-0215425) entitled "EPITOPE SYNCHRONIZATION IN ANTIGEN PRESENTING CELLS", which is hereby incorporated by reference in its entirety. Epitopes and epitope clusters for many of the TAA mentioned herein have been previously disclosed in PCT Publication No. WO 02/081646; in Patent Application No. 09/561,571; in U.S. Patent Application No. 10/117,937 (now abandoned), filed on April 4, 2002; U.S. Provisional Application Nos. 60/337,017 filed on November 7, 2001, and 60/363,210 filed on March 7, 2002, all entitled EPITOPE SEQUENCES, which are all incorporated by reference in their entirety. The teachings and embodiments disclosed in said publications and applications are contemplated as supporting principals and embodiments related to and useful in connection with the present invention.